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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,249	02/15/2002	Emanuela Mundo	10822-21	8612

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EXAMINER	
LYLES, JOHNALYN D	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,249	MUNDO ET AL.	
	Examiner	Art Unit	
	Johnalyn Lyles	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-11* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments filed in the response on 11/18/2004 under 37 CFR 1.312 have been entered.

2. Claims 8-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/18/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the susceptibility of Bipolar I or Bipolar II patients to antidepressant-induced mania related to Bipolar Disorder, wherein the antidepressant is the pro-serotonergic agent, does not reasonably provide enablement for determining the susceptibility of any patients to antidepressant-induced mania, wherein the patient is anyone treated with any antidepressant or where the antidepressant-induced mania is related to another mood or anxiety disorder, such as unipolar depression or obsessive-compulsive disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The

specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, lack of sufficient guidance in the specification and the breadth of the claims.

The claims as written are broad and encompass any patient and any antidepressant – induced mania induced by any antidepressant. The specification does not enable the broad scope of the claims, which encompasses all patient populations treated with any antidepressant and antidepressant-induced mania related to any disorders.

The specification teaches (page 6, lines 19-20) that the patient is any patient being treated with antidepressants, preferably a patient with Bipolar Disorder who is being treated with an antidepressant that acts directly or indirectly on the 5HTT sites. The specification discloses (page 1, lines 11-13) that induction of mania in patients treated with antidepressants is complex and has been described to occur in Bipolar (BP), Unipolar (UP), and Obsessive-Compulsive (OCD) disorders; however (page 1, lines 17-19), "more recently it has become clearer that the phenomenon of antidepressant-induced mania is strictly related to a diagnosis of BP." The specification also teaches (page 1, line 24-26) an antidepressant-induced manic episode occurs in patients with BP independent from the treatment status (antidepressant or electroconvulsive therapy), and (page 1, line 28-29) the rate of induction of mania is higher in BP patients treated with TCAs and MAOIs than in BP patients treated with SSRIs demonstrating that various antidepressants may produce differing incidences or occurrences of antidepressant-induced mania.

Furthermore, the art discloses that antidepressant-induced mania remains controversial; particularly antidepressant-induced mania lacks a consensus definition within the field as to what constitutes a switch into mania and how to reasonably attribute the switch to antidepressant use, may be associated with all antidepressants but with varying levels that may be patient-specific (Goldberg *et. al.*, 2003, *Bipolar Disorders*, 5:407-420), remains controversial in unipolar depression and may be the natural course of illness in bipolar patients (Chun *et. al.*, 2004, *Bipolar Disorders* 6:32-42).

The specification does not teach that the method can be practiced with antidepressant-induced mania related to other disorders, but discloses, "Antidepressant-induced mania is strictly related to a diagnosis of BP (page 1, line 18-19)". The specification does not teach the method can be practiced in patients with unipolar depression, obsessive-compulsive disorder, or all disorders treated with antidepressants. Finally, the specification does not teach that the method can be practiced with all possible antidepressants, which have different mechanisms of action, including selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline that increase serotonin levels; tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, and nortriptyline; monoamine oxidase inhibitors (MAOIs), such as anylcypromine and phenelzine, which block or inhibit, the action of the enzyme monoamine oxidase; and heterocyclics, such as bupropion and trazodone. Due to the large quantity of experimentation necessary to determine if other patients, including those specifically treated with antidepressants for disorders other than BP develop antidepressant-induced mania and antidepressants other than pro-serotonergic agents can be used, the lack of direction/guidance presented in the specification regarding whether the type of antidepressant treatment including dose effect the risk of

developing an antidepressant-induced mania and whether antidepressant-induced mania occurs with other disorders, the absence of working examples directed to same, the complex nature of the invention in which antidepressant-induced mania remains controversial as a bona fide form of mania or a side effect of drug therapy or a predisposed phenomenon, and the state of the prior art which established the unpredictability of antidepressant-induced mania related to other antidepressant disorders and the varying association with various antidepressants, and the breadth of the claims which fail to recite functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The specification provides essentially no guidance as to which of the essentially infinite possible patients is likely to be susceptible and the skilled artisan would not expect all patients or all patients using antidepressants to be susceptible to antidepressant-induced mania. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Mundo *et. al.* (abstract in *Biological Psychiatry*, 2000, 47(suppl):135S). Mundo *et. al.* teaches a method comprising obtaining a sample from a patient with Bipolar Disorder who was treated with a

proserotonergic agent and determining the presence of the s allele of the 5HTT polymorphism (See abstract). The abstract teachings meets the claim limitations because the abstract teaches a correlation between antidepressant induced mania and the 5HTT polymorphism by demonstrating an excess of the s allele in Bipolar Disorder patients with at least one pro-serotonergic drug induced manic episode (See abstract). Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et. al (US Patent App. No. 10/625134) in view of reference Bellivier *et. al.* (Neuroscience Letters, 1998, 255:143-46) and Mundo *et. al.* (abstract in *Biological Psychiatry*, 2000, 47(suppl):135S).

Williams *et. al.* teaches a method of screening human subjects for increased risk of disease by determining the serotonin transporter gene promoter genotype, with respect to long and short alleles thereof, of a subject which indicates whether or not the subject is at an increased risk of disease. The method comprises determining the presence of at least one serotonin transporter gene promoter long allele in a subject, wherein the presence of the allele indicates the subject is at an increased risk of disease. Williams *et. al.* teaches a method using a sample of blood, extracting nucleic acids from the sample using PCR and analyzing and detecting if the subject possesses the DNA corresponding to the long or short allele polymorphism by electrophoresis.

Williams *et. al.* does not teach a method for determining the susceptibility of a patient to a disease wherein the disease is a mental or psychiatric disease such as antidepressant-induced mania. Williams *et. al.* does not teach a patient that has Bipolar Disorder and is being treated with a pro-serotonergic antidepressant.

Bellivier *et. al.* teaches a method using a sample of blood, extracting nucleic acids from the sample using PCR and analyzing and detecting the polymorphism by electrophoresis in patients with Bipolar Disorder.

Mundo *et. al.* teaches the role of the serotonin transporter gene in antidepressant induced mania in Bipolar Disorder patients treated with proserotonergic agents. Mundo *et. al.* teaches a correlation between antidepressant induced mania and the 5HTT polymorphism by demonstrating an excess of the s allele in Bipolar Disorder patients with at least one pro-serotonergic drug induced manic episode.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the method of Williams *et. al.* and Bellivier et. al to determine the susceptibility of a Bipolar patient to antidepressant-induced mania because the methods use standard techniques for genotyping a polymorphism to determine susceptibility to a disease and Mundo *et. al.* established the necessary correlation to suggest determining the role of the polymorphism in the disorder. The person of ordinary skill in the art would have been motivated to make the modification because it is well-known in the art that Bipolar disorder has a significant genetic component (McGuffin and Katz, 1989, British Journal of Psychiatry, 155:294-304) as well as Mundo *et. al.* contemplates investigating the pharmacological response to selective serotonin reuptake inhibitors with respect to the 5HT transporter gene polymorphism (Am. J. Med. Genet., 2000, 96:379-383), and reasonably would have expected success because the serotonin transporter is the selective site of action of the proserotonergic agents used to treat bipolar disorder further suggesting a correlation in the transporter gene and the antidepressant-induced mania.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Johnalyn Lyles whose telephone number is 571-272-3433. The examiner can normally be reached on M-F 8 am - 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHARON L. TURNER, PH.D.
PATENT EXAMINER

jdl 2-12-05